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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|------------------------------|---------------------|------------------|
| 09/466,935 | 12/20/1999 | VITALIY ARKADYEVICH LIVSHITS | 0010-1070-0 | 1750 |
| 38108 | 7590 | 01/30/2004 | EXAMINER | |
| AJINOMOTO CORPORATE SERVICES, LLC INTELLECTUAL PROPERTY DEPARTMENT 1120 CONNECTICUT AVE., N.W. WASHINGTON, DC 20036 | | | STEADMAN, DAVID J | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1652 | |

DATE MAILED: 01/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------|------------------------|---------------------|
| Advisory Action | Application No. | Applicant(s) |
| | 09/466,935 | LIVSHITS ET AL. |
| | Examiner | Art Unit |
| | David J Steadman | 1652 |

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 25 November 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

- a) The period for reply expires 3 months from the mailing date of the final rejection.
- b) The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. The proposed amendment(s) will not be entered because:
 - (a) they raise new issues that would require further consideration and/or search (see NOTE below);
 - (b) they raise the issue of new matter (see Note below);
 - (c) they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
 - (d) they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3. Applicant's reply has overcome the following rejection(s): _____.
4. Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. The a) affidavit, b) exhibit, or c) request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attachment.
6. The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. For purposes of Appeal, the proposed amendment(s) a) will not be entered or b) will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: _____.

Claim(s) withdrawn from consideration: _____.

8. The drawing correction filed on _____ is a)a) approved or b)b) disapproved by the Examiner.
9. Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.
10. Other: _____.

ADVISORY ACTION

- [1] Claims 16-17 and 37-63 are pending in the application.
- [2] Claims 16-17 are in condition for allowance.
- [3] Claims 37-48 stand finally rejected.
- [4] Claims 49-63 are withdrawn from consideration as being drawn to a non-elected invention.
- [5] The written description rejection of claims 37-48 under 35 U.S.C. 112, first paragraph is maintained for the reasons of record and the reasons stated below. Applicants argue the characteristic of the instant invention does not lie in how the expression of the target DNA can be enhanced and instead is that enhanced expression of the target DNA results in an increased level of amino acid production. Applicants argue that a variety of methods of enhancing DNA expression were known at the time of the invention. Applicants argue that in view of the specification and the state of the art at the time of the invention, applicants were allegedly in possession of the claimed invention. Applicants' argument is not found persuasive.

Regarding applicants' argument that the "characteristic of the instant invention does not lie in how the expression of the target DNA can be enhanced", MPEP 2163 states, "[t]he claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art". In this case, the bacterial modification for increasing DNA expression as recited in the claims is an essential and critical feature of the claimed genus of bacteria and

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therefore, must be adequately described by the specification. In this case, the specification describes only a single modification that results in increased DNA expression, i.e., transformation of a bacterium with an expression vector encoding the target protein. While other methods of increasing DNA expression were well known in the art at the time of the invention (see below), the claims are not limited to such methods and broadly encompass species of bacteria that are modified to overexpress the target protein by any method. There is no dispute that increased DNA expression by transformation of a bacterium with an expression vector comprising said DNA or promoter substitution of an endogenous bacterial promoter with promoters that are well known in the art are all well-known methods for increasing the level and consequently, the activity of a given protein. However, in this case, the claims are NOT limited to bacteria having such modifications. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of

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species to reflect the variation within the genus. In this case, the specification discloses only two representative species of the claimed genus of modified bacteria, i.e., an *Escherichia* bacterium transformed with an expression vector comprising a nucleic acid encoding SEQ ID NO:4 and optionally transformed with an expression vector comprising a nucleic acid encoding SEQ ID NO:2. The specification fails to describe any additional representative species of the claimed genus. While MPEP § 2163 acknowledges that in certain situations “one species adequately supports a genus”, it is also acknowledges that “[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus”. In the instant case, the claimed genus of *Escherichia* bacteria encompasses species that are widely variant having any modification that results in increased DNA expression of a protein that makes the bacteria L-threonine resistant and optionally wherein increased DNA expression is a result of increased DNA copy number (by any modification) or promoter substitution (by any promoter). As such, the disclosure of the single representative species of an *Escherichia* bacterium transformed with an expression vector comprising a nucleic acid encoding SEQ ID NO:4 and optionally transformed with an expression vector comprising a nucleic acid encoding SEQ ID NO:2 is insufficient to be representative of the attributes and features of *all* species encompassed by the claimed genus of bacteria. Given the lack of description of a representative number of polynucleotides, the specification fails to sufficiently describe the claimed invention in such full, clear,

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concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[6] The scope of enablement rejection of claims 37-48 under 35 U.S.C. 112, first paragraph is maintained for the reasons of record and the reasons stated below.

Applicants argue that a variety of methods of enhancing DNA expression were known at the time of the invention and that one skilled in the art can select a well-known method for increasing expression that would not require undue experimentation. Applicants argue that in view of the specification and the state of the art at the time of the invention, the claimed bacteria can be made and used without undue experimentation. Applicants' argument is not found persuasive.

The examiner maintains that the scope of claimed bacteria is not enabled by the specification and the prior art according to the detailed analysis of the Factors of *In re Wands* as set forth at pages 6-8 of the Office action mailed March 25, 2003 and undue experimentation would be required for a skilled artisan to make the entire scope of claimed bacteria. As stated above, there is no dispute that increased DNA expression by transformation of a bacterium with an expression vector comprising said DNA or promoter substitution of an endogenous bacterial promoter with a well-known promoter are all well-known methods for increasing the level and therefore activity of a given protein. However, neither the specification nor the specification in combination with the prior provides guidance that would enable the broad scope of claimed modified bacteria. Instead, the claims are so broad as to encompass *all Escherichia* bacteria having *any* modification that results in increased DNA expression of a protein that makes the

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bacteria L-threonine resistant and optionally wherein increased DNA expression is a result of increased DNA copy number (by *any* modification) or promoter substitution (by *any* promoter). Based on the detailed analysis of the Factors of *In re Wands* as set forth at page 6-8 of the Office action mailed March 25, 2003, the specification in combination with the prior art fails to enable the broad scope of claimed bacteria. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as described in a detailed analysis of the Factors of *In re Wands* as set forth at pages 6-8 of the Office action mailed March 25, 2003, and for the reasons stated above, undue experimentation is necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652


REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1600
(Handwritten signature)